

Online Research @ Cardiff

This is an Open Access document downloaded from ORCA, Cardiff University's institutional repository: <https://orca.cardiff.ac.uk/id/eprint/130974/>

This is the author's version of a work that was submitted to / accepted for publication.

Citation for final published version:

Cunningham, Adam, Fung, Wilson, Massey, Thomas ORCID:
<https://orcid.org/0000-0002-9804-2131>, Hall, Jeremy ORCID:
<https://orcid.org/0000-0003-2737-9009>, Owen, Michael ORCID:
<https://orcid.org/0000-0003-4798-0862>, Van Den Bree, Marianne ORCID:
<https://orcid.org/0000-0002-4426-3254> and Peall, Kathryn ORCID:
<https://orcid.org/0000-0003-4749-4944> 2020. Movement disorder phenotypes
in children with 22q11.2 deletion syndrome. *Movement Disorders* 35 (7) , pp.
1272-1274. 10.1002/mds.28078 file

Publishers page: <http://dx.doi.org/10.1002/mds.28078>
<<http://dx.doi.org/10.1002/mds.28078>>

Please note:

Changes made as a result of publishing processes such as copy-editing, formatting and page numbers may not be reflected in this version. For the definitive version of this publication, please refer to the published source. You are advised to consult the publisher's version if you wish to cite this paper.

This version is being made available in accordance with publisher policies.

See

<http://orca.cf.ac.uk/policies.html> for usage policies. Copyright and moral rights for publications made available in ORCA are retained by the copyright holders.



Movement Disorder Phenotypes in Children With 22q11.2 Deletion Syndrome

The 22q11.2 deletion syndrome (22q11.2DS) is associated with a broad spectrum of clinical phenotypes, including congenital heart defects and immune deficiencies. In addition, there is also an increased risk of psychiatric disorders, cognitive deficits, and functional motor impairments.^{1–3} To date, a systematic examination of movement disorders has not been undertaken in this group.

Nineteen participants with 22q11.2DS (11 male; 8 female; median age, 12.7 years; range, 6.8–17.1 years), and 13 sibling controls (7 male; 6 female; median age, 11.2 years; range, 7.5–17.5 years) were recruited following informed consent, via ongoing cohort studies at Cardiff University (CU) with no further selection criteria applied. Ethical approval was provided by CU School of Medicine Research Ethics (reference: 17/69). The presence of the 3-Mb 22q11.2 deletion was confirmed using the Infinium PsychArray-v1.1 (Illumina) platform, fluorescence in situ hybridization or genetic arrays through the National Health Service medical genetics departments.

Data collected included sex, age at examination, medical comorbidities, and developmental history alongside assessment of

full-scale intelligence quotient (IQ), psychiatric symptoms, and coordination performance. Motor assessment involved a standardized videotaped clinical examination using a modified Burke-Fahn-Marsden Dystonia (BFMDRS) rating scale protocol.⁴ Examinations were reviewed independently by 3 neurologists blinded to all clinical information. Reviewers indicated if a movement disorder was observed and determined its phenomenology and body distribution. A movement disorder was considered present when there was agreement between all neurologists. Statistical analysis was carried out in R, using Fisher's exact tests, chi-squared tests, Pearson's correlations, and *t* tests as appropriate.

Sample demographics are presented in Table 1. There was a higher rate of movement disorders in the 22q11.2DS group compared with controls ($P = 0.0002$), with consensus agreement for a movement disorder in 18 of 19 children with 22q11.2DS (94.7%) compared with 4 of 13 of controls (30.8%). Dystonia was the most common movement disorder subtype, in isolation (94.4%, $n = 17$) and combined with upper limb distal jerks (5.6%, $n = 1$). The limbs and craniocervical region were most commonly affected, with upper limb involvement in all 18 cases (Videos 1–3). Three of 4 controls displayed isolated dystonia, with upper limb involvement in all 4. In the 22q11.2DS cohort, dystonia severity was mild (mean BFMDRS, 24.93/120) but was associated with lower IQ ($r = -0.52$, $P = 0.03$) and higher anxiety symptoms ($r = 0.57$, $P = 0.03$).

This is the first cohort study investigating the prevalence and type of movement disorders in young people with 22q11.2DS. Dystonia was the most commonly observed subtype, although these features were mild and tended to be associated with action. Identification of true movement disorders is often challenging in this age range, but the frequency of dystonic signs in the 22q11.2DS group indicate that they were associated with the 22q11.2DS phenotype, rather than neuromotor immaturity. More severe dystonia was associated with lower IQ and higher levels of anxiety. The 22q11.2 deletion is known to affect brain development,^{5,6} and genes in the region such as *COMT* are expressed in the brain.⁷ Our study is a cross-sectional, longitudinal examination throughout childhood, adolescence, and into adult-life and is required to gain a more comprehensive understanding of the 22q11.2DS motor phenotype. Although this cohort is relatively small, the high rate and preponderance of dystonia indicate that it is likely part of the neurodevelopmental phenotype of 22q11.2DS.

Author Contributions

Adam C Cunningham had a major role in the acquisition of data; interpreted the data; and drafted the article for intellectual content. Wilson Fung had a major role in the acquisition of data and revised the article for intellectual content. Thomas H. Massey had a major role in the acquisition of data and revised the article for intellectual content. Jeremy Hall interpreted the data and revised the article for intellectual content. Michael J. Owen interpreted the data and revised the article for intellectual content. Marianne B. M. van den Bree designed and conceptualized the study, interpreted the data, and revised the article for intellectual content. Kathryn J. Peall designed

© 2020 The Authors. *Movement Disorders* published by Wiley Periodicals, Inc. on behalf of International Parkinson and Movement Disorder Society.

This is an open access article under the terms of the Creative Commons Attribution License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.

*Correspondence to: Dr. Kathryn Peall, Neuroscience and Mental Health Research Institute, Cardiff University, Hadyn Ellis Building, Maindy Road, Cardiff, CF24 4HQ, UK; E-mail: peallkj@cardiff.ac.uk

Marianne B. M. van den Bree and Kathryn J. Peall contributed equally to this work.

Relevant conflicts of interest/financial disclosures: Drs Cunningham, Fung, Massey, and Peall report no financial disclosures. Professors Hall, Owen, and van den Bree are supported by a collaborative research grant from Takeda Pharmaceutical Company Limited. Takeda played no part in the conception, design, implementation, or interpretation of this study, and there is no benefit to them in relation to the published work.

Funding agencies: This research was funded by the Medical Research Council (MR/N022572/1 and MR/L011166/1), by the Baily Thomas Charitable Trust (2315/1), the Waterloo Foundation (918-1234), the National Institute for Mental Health (5U01MH101724), Wellcome Trust Strategic Award (503147), Health & Care Research Wales (Welsh Government, 507556), Medical Research Council Centre grant (G0801418), Medical Research Council Programme grant (G0800509), and an Early Career Research Fellowship from the Waterloo Foundation awarded to A.C.C. T.H.M. is funded by an MRC Post-Doctoral Clinical Research Fellowship. K.J.P. is funded by an MRC Clinician-Scientist Fellowship (MR/P008593/1).

Received: 6 February 2020; **Revised:** 27 March 2020; **Accepted:** 6 April 2020

Published online 00 Month 2020 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/mds.28078

TABLE 1. Cohort demographic, motor, and nonmotor characteristics

	22q11.2DS n (%) / mean (SD)	Sibling controls n (%) / mean (SD)	22q11.2DS versus sibling controls P (95% CI)	22q11.2DS cohort: correlation analysis with BFMDRS severity Scores Correlation coefficient, r (P)
Total cohort (M : F)	19 (11:8)	13 (7:6)	—	
Age at examination (years), Median (range)	12.70 (6.8–17.1)	11.12 (7.5–17.5)	0.79 (–2.8 to 2.2)	–0.24 (0.34)
FSIQ	78.83 (10.06)	109 (15.13)	<0.0001 (21.16–39.64)	–0.52 (0.03)
BFMDRS severity score (maximum possible score, 120)	24.93 (8.17)			
Medication				
≥1 Medication prescribed	12 (63.2%)	0 (0%)	0.0004^b	
Melatonin	5 (26.3%)	—	—	
Antibiotics	4 (21.1%)	—	—	
Laxatives	3 (15.8%)	—	—	
Vitamin/mineral supplementation	3 (15.8%)	—	—	
Antidepressants	1 (5.3%)	—	—	
Medical comorbidities				
Cardiac defect	13 (68.4%)	0 (0%)	0.0001	
ASD/VSD	5 (26.3%)	—	—	
Tetralogy of Fallot	4 (21.1%)	—	—	
Other	4 (21.1%)	—	—	
Past/present seizures	1 (5.3%)	0 (0%)	>0.99	
Cleft lip/palate	6 (31.6%)	0 (0%)	0.06	
Recurrent respiratory infections	7 (36.8%)	0 (0%)	0.02	
Recurrent ear infections	6 (31.6%)	1 (7.7%)	0.20	
Psychiatric symptoms				
ADHD	7 (36.8%)	1 (7.7%)	0.10	
Anxiety disorder (overall)	5 (26.3%)	1 (7.7%)	0.36	
Social phobia	3 (15.8%)	0 (0%)	0.25	
Generalized anxiety disorder	1 (5.3%)	0 (0%)	>0.99	
Specific phobia	1 (5.3%)	1 (7.7%)	>0.99	
ADHD count score	3.39 (3.38)	1.00 (3.16)	0.07 (–2.39 to 1.3)	0.41 (0.10)
Anxiety count score	2.13 (3.18)	1.75 (2.96)	0.78 (–3.17 to 2.42)	0.57 (0.03)
Autism trait symptoms score	11.43 (5.16)	2.50 (2.27)	<0.0001 (–12.55 to –5.30)	0.42 (0.16)
Developmental history				
Preterm birth	4 (21.1%)	5 (38.5%)	0.43	
Failure to thrive	8 (42.1%)	0 (0%)	0.01	
Feeding difficulties	16 (84.2%)	1 (7.7%)	<0.0001	
Parental reported clumsiness	15 (78.9%)	3 (23.1%)	0.003	
Talking by 2 years of age	6 (31.6%)	12 (92.3%)	0.0009	
Walking by 1.5 years of age	11 (57.9%)	11 (84.6%)	0.14	
Statement of educational needs/education and health care plan	13 (68.4%)	1 (7.7%)	0.0009	
Age at riding a bike (years), median (range)	6.5 (5–10)	5 (3.5–7)	0.09 (–27.6 to 2.1)	0.02 (0.95)
Age at being able to button (years), median (range)	6.2 (3.5–10.25)	4 (3–6.5)	0.008 (–41.6 to –7.0)	–0.10 (0.79)
Age at being able to do laces (years), median (range))	9.75 (6–11)	6.9 (5–8.7)	0.008 (–47.3 to 8.4)	0.20 (0.63)
Movement disorder				
Evidence of movement disorder on examination	18 (94.7%)	4 (30.8%)	0.0002	
Dystonia	17 (94.4%)	3 (23.1%)	0.0002	
Distal UL jerks (possible myoclonus/ possible chorea)	1 (5.6%)	1 (7.7%)	>0.99	
Body part affected				
Eyes	0 (0%)	0 (0%)	>0.99 ^b	
Oromandibular region	6 (31.6%)	0 (0%)	0.0^b	
Cervical	8 (42.1%)	1 (7.7%)	0.05	
Upper limbs	18 (94.7%)	4 (30.8%)	0.0002	
Trunk	0 (0%)	0 (0%)	>0.99	
Lower limbs	8 (42.1%)	3 (23.1%)	0.45	

(Continues)

TABLE 1. Continued

	22q11.2DS n (%) / mean (SD)	Sibling controls n (%) / mean (SD)	22q11.2DS versus sibling controls <i>P</i> (95% CI)	22q11.2DS cohort: correlation analysis with BFMDRS severity Scores Correlation coefficient, <i>r</i> (<i>P</i>)
DCDQ scores				
Overall	37.37 (12.54)	69.75 (6.90)	<0.0001 (24.27–40.49)	−0.29 (0.24)
Control during movement	15.21 (5.35)	28.17 (2.89)	<0.0001 (9.51–16.4)	−0.11 (0.65)
Fine motor score	10.95 (3.63)	19.33 (1.44)	<0.0001 (6.13–10.64)	−0.41 (0.09)
General coordination score	11.21 (5.34)	22.25 (3.98)	<0.0001 (7.4–14.7)	−0.29 (0.23)


ADHD, attention deficit hyperactivity disorder; DCDQ, Developmental Coordination Disorder Questionnaire; FSIQ, full-scale intelligence quotient; SCQ, Social Communication Questionnaire; UL, upper limbs; Control during movement, fine motor score, and general coordination score all form subsections of the DCDQ. The SCQ is used to measure Autism Trait Symptom Score, ADHD, and anxiety symptoms were measured using the Child and Adolescent Psychiatric Assessment (CAPA).

Bold denotes $P \leq 0.05$.

and conceptualized the study, analyzed the data, and drafted the article for intellectual content.

Statistical analysis undertaken by A.C.C. and K.J.P. (both Cardiff University, UK).

Search terms: [161] All Movement Disorders, [162] Dystonia, [228] Developmental Disorders, [230] Child Psychiatry, [91] All Genetics. ■

Adam C. Cunningham, PhD,¹  Wilson Fung, MD,² 
 Thomas H. Massey, MD, PhD,¹ Jeremy Hall, MD, PhD,^{1,3}
 Michael J. Owen, MD, PhD,^{1,3}
 Marianne B. M. van den Bree, PhD,^{1,3} and
 Kathryn J. Peall, MD, PhD^{3*}

¹MRC Centre for Neuropsychiatric Genetics and Genomics,
 Division of Psychological Medicine and Clinical Neurosciences,
 Cardiff University School of Medicine, Cardiff, UK

²Aneurin Bevan University Health Board, Royal Gwent Hospital,
 Newport, UK

³Neuroscience and Mental Health Research Institute, Division of
 Psychological Medicine and Clinical Neurosciences, Cardiff
 University School of Medicine, Cardiff, UK

References

1. McDonald-McGinn DM, Sullivan KE, Marino B, et al. 22q11.2 deletion syndrome. *Nat Rev Dis Primers* 2015;1:15071.

2. Schneider M, Debbané M, Bassett AS, et al. Psychiatric disorders from childhood to adulthood in 22q11.2 deletion syndrome: Results from the international consortium on brain and behavior in 22q11.2 deletion syndrome. *Am J Psychiatry* 2014; 171:627–639.
3. Cunningham AC, Delpont S, Cumines W, et al. Developmental coordination disorder, psychopathology and IQ in 22q11.2 deletion syndrome. *Br J Psychiatry* 2018;212:27–33.
4. Burke RE, Fahn S, Marsden CD, et al. Validity and reliability of a rating scale for the primary torsion dystonias. *Neurology* 1985;35: 73–77.
5. Sun D, Ching CRK, Lin A, et al. Large-scale mapping of cortical alterations in 22q11.2 deletion syndrome: Convergence with idiopathic psychosis and effects of deletion size. *Mol Psychiatry* 2018; <https://doi.org/10.1038/s41380-018-0078-5>
6. Ching CRK, Gutman BA, Sun D, et al. Mapping Subcortical Brain Alterations in 22q11.2 Deletion Syndrome: Effects of Deletion Size and Convergence With Idiopathic Neuropsychiatric Illness. *Am J Psychiatry* 2020; <https://doi.org/10.1176/appi.ajp.2019.19060583>
7. Meechan DW, Maynard TM, Tucker ES, et al. Modeling a model: Mouse genetics, 22q11.2 Deletion Syndrome, and disorders of cortical circuit development. *Prog Neurobiol* 2015;130:1–28.

Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.